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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02019406.4

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R C van Dijk

PCT/EP 03/04662

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Anmeldung Nr:
Application no.: 02019406.4
Demande no:

Anmeldetag:
Date of filing: 30.08.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

ALTANA Pharma AG
Byk-Gulden-Str. 2
78467 Konstanz
ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
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If no title is shown please refer to the description.
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Novel combination

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

A61K31/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

Novel Combination

Technical Field of the Invention

The present invention is related to a novel combination of ciclesonide and antihistamines for use in drug therapy in particular in the treatment of allergic rhinitis. In particular the novel combination is administered in the form of an aqueous pharmaceutical composition that contains ciclesonide and antihistamine and having an osmotic pressure of less than 290 mOsm.

Background Art

Allergic rhinitis is a common disorder and the number of patients is steadily increasing. The disease is caused by ambient airborne allergens, which cause an allergic inflammation within the nasal mucosa and it is often accompanied by conjunctivitis. According to the allergen, the allergic rhinitis is subdivided into seasonal allergic rhinitis (allergens like grass pollen, cedar pollen) and perennial allergic rhinitis (indoor allergens like mould, allergens from animals and house dust mite). Allergic rhinitis has a great impact on the quality of life. The patients suffer from an itchy and running nose, nasal blockage, headache and fatigue.

The current treatment of allergic rhinitis is mainly focused on symptomatic relief. Oral and to a lesser extent topical antihistamines are the most widely used remedies. Oral antihistamines alleviate the histamine driven symptoms only. Allergen contact causes degranulation of mucosal mast cells and histamine is released. Histamine is responsible for the itching and sneezing and the increase in nasal secretion. Antihistamines block the binding of histamine to the histamine-H1-receptor and thereof the histamine mediated symptoms. Beside this obvious pathway, the allergens cause an eosinophilic inflammation of the nasal mucosa, which is mainly responsible for symptoms like nasal hyperreactivity, nasal blockage and the fear of the so called change of floors, which means that an untreated allergic rhinitis can develop to sinusitis and asthma bronchiale.

Treatment with glucocorticoids is currently the only one therapy, which targets the underlying allergic inflammation. To avoid systemic side effects typically for glucocorticoids, e.g. immunosuppression, reduced protein synthesis, impaired growth in children, topical treatment with glucocorticoids is the preferred way of administration.

A disadvantage of nasal steroids is the slow onset of action and the need for continuous treatment. It takes 4-6 days of continuous treatment before a symptom relief can be observed. Therefore, the patients are recommended to begin to take glucocorticoids before the pollen season starts. The slow onset of action, the need of consequent treatment and the fear of steroid induced side effects have a negative impact on the use of intranasal steroids and patient's compliance.

Other medications available for the treatment are just for symptomatic relief, for example intranasal muscarinic antagonists (ipratropium to reduce nasal secretion), adrenoreceptor agonists (xylometazoline to reduce nasal congestion).

WO 97/01337 describes a nasal spray or nasal drops formulation comprising beclomethasone, flunisolide, triamcinolone, dexamethasone or budesonide in combination with the antihistamines levocabastine, azelastine or azatadine and sterile water.

WO01/22955 is related to a novel combination of loteprednol, a so-called soft steroid with antihistamines.

Detailed Description of the invention

Surprisingly it has now been found that combined administration of ciclesonide and at least one antihistamine results in a very effective and safe treatment of symptoms accompanied with allergic rhinitis. By combined administration of the ciclesonide and the antihistamine as hypotonic aqueous pharmaceutical formulation a rapid onset of action and quick symptom relief is observed without the fear of glucocorticoid like side effects. By administering the hypotonic aqueous pharmaceutical composition according to the invention to the nasal mucosa the active ingredients rapidly enter the nasal mucosa and have a very long retention time. Therefore very low doses of ciclesonide and a once-daily, maximal twice-daily treatment is necessary to achieve an effective treatment.

The present invention therefore relates to an aqueous pharmaceutical composition for the treatment of allergic rhinitis for application to the mucosa comprising as active ingredients a combination of at least one antihistamine and ciclesonide together with one or more water-insoluble and/or water-low soluble substance and having an osmotic pressure of less than 290 mOsm. Preferably the osmotic pressure is 150 mOsm or lower, more preferably 72 mOsm or lower, more preferably 60 mOsm or lower, more preferably 40 mOsm or lower, more preferably 30 mOsm or lower, still more preferably 20 mOsm or lower and most preferably 10 mOsm or lower.

According to the present invention it is not particularly required to add a substance for controlling osmotic pressure (osmotic pressure-controlling agent) but when it is added any substance can be used. In the present invention, a substance for controlling osmotic pressure (osmotic pressure controlling agent) can be added to control osmotic pressure, specific examples of which include salts such as sodium chloride and water-soluble sugars such as glucose, with glucose being a particularly preferable example.

In a preferred embodiment the pharmaceutical composition is a pharmaceutical composition as described for ciclesonide in WO 01/28562 or WO 01/28563.

The water-insoluble or water-low soluble substance may be any substance, and preferred examples include celluloses and more preferably crystalline celluloses. According to the present invention, the concentration of water-insoluble and/or water-low soluble substance present in form of solid particles in an aqueous medium is preferably 0.3% w/w and above, and particularly preferably 0.5% w/w to 5% w/w, relative to the total amount of the composition.

In addition, an aqueous polymer substance can also be added in the present pharmaceutical composition. Specific examples of such include propylene glycol alginate, pectin, low methoxyl pectin, gua gum, gum Arabic, carrageenan, methyl cellulose, carboxymethyl cellulose sodium, xanthan gum hydroxypropylmethyl cellulose and hydroxypropyl cellulose, while particularly preferable examples include carboxymethyl cellulose sodium, polyethylene glycol and hydroxypropyl cellulose. Carboxymethyl cellulose sodium blended with microcrystalline cellulose, is an example of a combination of these water-soluble substance and water-insoluble substance that can be used in the present invention. Furthermore, in the case of adding these water-soluble polymer substances, the concentration of said substance is preferably 1% w/w to 30 % w/w relative to the water-insoluble substance and/or water-low soluble substance.

In a preferred embodiment of the invention hydroxypropylmethyl cellulose is contained in the pharmaceutical compositions according to the invention. The hydroxypropylmethyl cellulose may be any grade, a specific example is hydroxypropylmethyl cellulose 2910. Although said hydroxypropylmethyl cellulose may be present at any concentration, its concentration is preferably from 0.001 % w/w to 30 % w/w, particularly preferably form 0.01 % w/w to 5 % w/w, more particularly preferably from 0.01 % w/w to 1 % w/w, and most preferably from 0.01 % w/w to 0.5 % w/w, relative to the total amount of composition.

A surfactant and/or wetting agent, although not essential in the present invention, can be added, specific examples of which include Polysorbate 80, glycerin monosterarate, polyoxyl stearate, lauromacrogol, sorbitan oleate and sucrose fatty acid esters.

An effective amount of ciclesonide and the topical antihistamine used in the present invention can be determined according to the type and degree of the respective disease, as well as the age and body weight of the patient, and so forth. Preferably the pharmaceutical composition according to the invention is administered as one to four sprays per nostril once or twice a day. The dose of ciclesonide per actuation is expediently from 10 μg to 400 μg, preferably 20 μg to 200 μg. The dose of the antihistamine per actuation is expediently from 10 μg to 500 μg, preferably 25 μg to 250 μg.

Ciclesonide is the INN for a compound with the chemical name [11β,16α(R)]--16,17-[(Cyclohexylmethylen)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-dien3,20-dion. Ciclesonide and its preparation are disclosed in DE 4129535. Ciclesonide as used herein also includes, solvates of ciclesonide, physiological functional derivatives of ciclesonide or solvates thereof.

Physiological functional derivatives of ciclesonide which may be mentioned in connection with the invention are expediently chemical derivatives of ciclesonide which have similar physiological function as compared to ciclesonide, for example the 21-hydroxy derivative of ciclesonide with the chemical name 16α,17-(22R,S)-Cyclohexylmethylendioxy-11β,21-dihydroxypregna-1,4-dien-3,20-dion. This compound and its preparation are disclosed in WO 9422899.

Preferably ciclesonide is dispersed in the aqueous medium in form of solid particles.

The concentration of ciclesonide of the present invention is preferably from 0.01 % w/w to 1 % w/w, and particularly preferably from 0.05 w/w to 0.5 % w/w, relative to the total amount of the composition.

Although the ciclesonide particles that can be used in the present invention may be of any size, they are preferably within the range of 10 nm to 100 μm, and particularly preferably within the range of 100 nm to 10 μm.

Antihistamines which may be mentioned in connection with the invention are azelastin or levocabastin. The antihistamine may also be present in form of a pharmaceutically acceptable salt. The hydrochlorides may be mentioned as examples. In case of water soluble antihistamines such as azelastin hydrochloride the antihistamine will be dissolved in the pharmaceutical compositions according to the invention.

The concentration of the topical antihistamine is preferably from 0.01 % w/w to 0.5 % w/w, and particularly preferably from 0.05 w/w to 0.2 % w/w, relative to the total amount of the composition.

Any method for dispersing a water-insoluble substance and/or water-low soluble substance in an aqueous medium may be used for the production of the aqueous pharmaceutical composition according to the invention, a specific example of which is a method that uses a homomixer.

Known antiseptics, pH controlling agents, preservatives, buffers, colorants, smell corrigents and so forth may be added as necessary to the compositions of the present invention to improve its physical properties, stability, appearance or odor and so forth of the formulation.

Examples of antiseptics include benzalkonium chloride, examples of pH controlling agents include hydrochloric acid and sodium hydroxide, examples of preservatives include potassium sorbate, examples of buffers include phosphoric acid and its salt, examples of colorants include red dye no. 2, and examples of smell corrigents include menthol.

Due to the unique galenic formulation, ciclesonide rapidly enters the nasal mucosa and has a very long retention time. Therefore, very low doses of ciclesonide and the once daily, maximal twice-daily treatment is necessary to achieve an effective treatment. A low dose of ciclesonide in a hypotonic watery

suspension in combination with a topical antihistamine (e.g. azelastine or levocabastine) results in a very effective and safe treatment of all symptoms accompanied with allergic rhinitis. A clear advantage of this combination is the rapid onset of action and quick symptom relief without the fear of glucocorticoid like side effects.

When given to the nasal mucosa the present invention may be filled into plastic or glass bottles which are fitted with a metering atomising pump and a nasal adapter.

Examples

Ciclesonide aqueous pharmaceutical compositons containing the components indicated below are prepared by processing with a homomixer. Homomixer processing is performed, e.g., at 6000 rpm for 30 minutes.

Example 1: Combination of Ciclesonide and Azelastine Hydrochloride

Ciclesonide:	0.05%
Azelastine hydrochloride	0.14%
Microcrystalline cellulose and carboxymethyl cellulose sodium	1.7%
Hydroxypropylmethyl cellulose 2910	0.1%

Each 100 mg spray delivered by a nasal applicator delivers 50 µg of ciclesonide and 140 µg of azelastine hydrochloride.

Example 2: Combination of Ciclesonide and Levocabastine Hydrochloride

Ciclesonide:	0.05%
Levocabastine hydrochloride	0.054%
Microcrystalline cellulose and carboxymethyl cellulose sodium	1.7%
Hydroxypropylmethyl cellulose 2910	0.1%

Each 100 mg spray delivered by a nasal applicator delivers 50 µg of ciclesonide and 54 µg of levocabastine hydrochloride (equivalent to 50 µg levocabastine).

Patent Claims

1. Aqueous pharmaceutical composition for the treatment of allergic rhinitis for application to the mucosa, comprising as active ingredients a combination of at least one antihistamine and ciclesonide together with one or more water-insoluble and/or water-low soluble substance and having an osmotic pressure of less than 290 mOsm.

2. The pharmaceutical composition for application to the mucosa according to claim 1, wherein said osmotic pressure is 150 mOsm or less.

3. The pharmaceutical composition for application to the mucosa according to claim 1, wherein said osmotic pressure is 60 mOsm or less.

4. The pharmaceutical composition for application to the mucosa according to claim 1, wherein said osmotic pressure is 40 mOsm or less.

5. The pharmaceutical composition for application to the mucosa according to claim 1, wherein said osmotic pressure is 20 mOsm or less.

6. The pharmaceutical composition for application to the mucosa according to claim 1, further comprising an osmotic pressure-controlling agent.

7. The pharmaceutical composition for application to the mucosa according to claim 1, wherein said water-insoluble and/or water-low soluble substance is a cellulose.

8. The pharmaceutical composition for application to the mucosa according to claim 7, wherein said cellulose is microcrystalline cellulose.

9. The pharmaceutical composition for application to the mucosa according to claim 1, wherein said one or more water-insoluble and/or water-low soluble substance is present as solid particles in an aqueous medium.

10. The pharmaceutical composition for application to the mucosa according to claim 1, further comprising a water-soluble polymer substance.

11. Pharmaceutical composition for application to the mucosa according to claim 10, wherein the combination of said water-insoluble substance and water-soluble polymer is microcrystalline cellulose and carboxymethyl cellulose sodium.

12. The pharmaceutical composition for application to the mucosa according to claim 1, further comprising a surfactant and/or a wetting agent.

13. The pharmaceutical composition for application to the mucosa according to claim 1, wherein said mucosa is nasal mucosa.

14. Pharmaceutical composition according to claims 1 through 9, wherein the antihistamine is azelastine, levocabastine, a salt or solvate thereof.

15. Use of ciclesonide in combination with at least one antihistamine for the manufacture of a pharmaceutical composition for the treatment of allergic rhinitis.

Abstract

The present invention relates to a combination of ciclesonide with antihistamines.